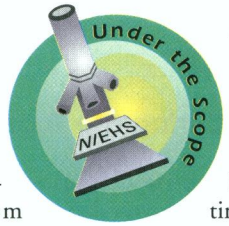
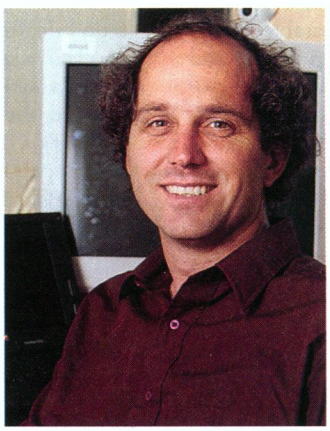
Risk Assessment: Bridging the Gap between Prediction and Experimentation



Much of modern science concentrates on protecting people from potentially harmful chemicals, such as pesticides and herbicides. Safeguarding humans from unhealthy exposures usually includes two problematic steps. First, humans often experience low-level exposures to a compound, but human risk must be determined from experiments that employ high-level exposures. Second, scientists must extrapolate from a chemical's effect on rodents—the traditional experimental subjects—to humans. The NIEHS Laboratory of Computational Biology and Risk Analysis (CoBRA) is working to solve the problems associated with these steps by designing models to interpret the available data, so that the resulting knowledge can be applied to risk-prediction models.

Designing such a model for a specific system—for example, a particular compound's carcinogenic characteristics—involves a multistep approach. According to Christopher J. Portier, chief of CoBRA, "We start with existing models. Never reinvent the wheel—that's my belief." Portier and his colleagues search the scientific literature for information on that particular system. Existing models of how a system works and additional information from the literature can be combined to form a modified model. Whenever possible, such a model quantifies each step in a system. Portier says his laboratory's models use "any and all" mathematics, including simple, curve-fitting techniques, image-analysis techniques, neural networks, nonlinear dynamic systems, standard geometry, chaos models, and stochastic models. After arranging a model's steps and transforming them into mathematical equations, Portier and his colleagues write a computer program that runs the available data through the model. The program helps answer a critical question: do the available data make sense, given the model. If the answer is no, the investigators reject the model; if the answer is yes, the investigators conclude that the model may be accurate—until new data force them to do further fine-tuning or even start over.

Making use of such models depends on collaboration. "A mathematician who sits in an office and does modeling all day without talking to anyone is going to develop a lot of nice models that no one's going to use," Portier says. "Part of the utility is tying models to what researchers themselves are saying. We need to interact with them, to get their ideas." In addition to a wide range of contacts at the NIEHS, CoBRA researchers are collaborating with a variety of other groups, including the EPA, the National Toxicology Program (NTP), and foreign governments, including those of Australia, Finland, and Korea.


Steve McCaw, Image Associates, Inc.

Christopher J. Portier

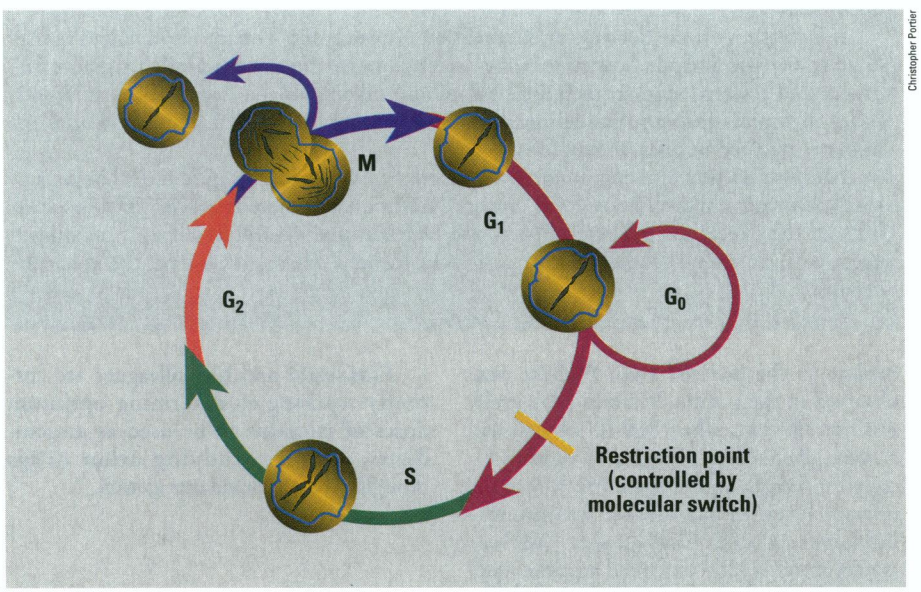
All CoBRA projects focus on three questions: how do you predict human risk from available data, what is the overall quality of the resulting predictions, and what data should be collected by the NTP to make even better predictions in the future. Two general areas of research at CoBRA—development of new methods and model-directed designs—are providing improved answers to these fundamental questions.

New Methods

Improved knowledge about human risk often comes from new methods of data analysis. In some cases, new methods may be developed to improve the way that existing data can be analyzed. In other cases, new methods must be developed to handle novel approaches.

"New techniques, new methods, and new data emerge constantly," Portier says, "but it's not always clear how they can be used in risk assessment. We want to understand their utility. Part of that sometimes means we have to go back to the researchers and say, 'You're collecting the wrong data; this is really what we need. Can you do this?'. Another part of it is helping the researchers get better information for use in the regulatory arena and, at the same time, understanding what the data might mean for human health;" for instance, figuring out what new biochemical findings about the cell cycle might mean for risk assessment.

Hisham El-Masri, a postdoctoral trainee at CoBRA, says, "We are working to incorporate all phases of the cell cycle—starting from G_0, G_1, S, G_2, and M—into a model that describes the transition of cells from one phase to the next." The model will include known biochemical steps that trigger a cell to move from one phase to another. So far, El-Masri has concentrated on modeling specific pieces of the cell cycle. For example, one piece models the effect of growth factors on the transition from G_0, the

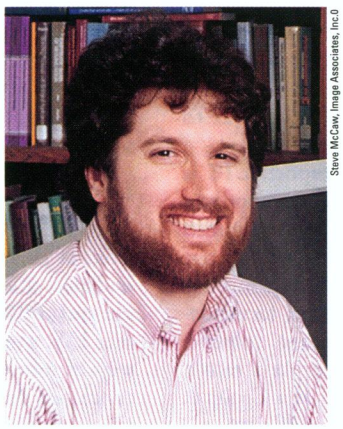


Christopher Portier

Putting numbers into pictures. Researchers in the Laboratory of Computational Biology and Risk Analysis are using information on how the cell cycle is controlled to develop baseline mathematical models for risk assessment.

resting phase, to G_1, and another models the effect of several proteins—cyclins, cdcs and cdks—on the transition from G_1 to S (the stop phase). Eventually, El-Masri and Portier expect to combine several of these smaller models into a complete model of the cell cycle, which will be compared against experimental data. If the model makes sense in terms of the available data, it could be used in risk assessment—particularly for chemicals that affect cell division.

Building a quantitative model of cell-cycle kinetics may provide several benefits. It will help scientists to understand how the current breakthroughs in the signaling process are linked together, creating a flow chart, of sorts, of the controls of the cell cycle. The model will also show how specific gene mutations affect the cell cycle. The cell-cycle model will then be incorporated into a comprehensive model of carcinogenesis. For example, El-Masri says, "We can start with a chemical like dioxin and then follow it all the way down to its effect on the distribution of cells in each phase. That could be quantitatively incorporated into a risk assessment for the effect of dioxin on cell proliferation."



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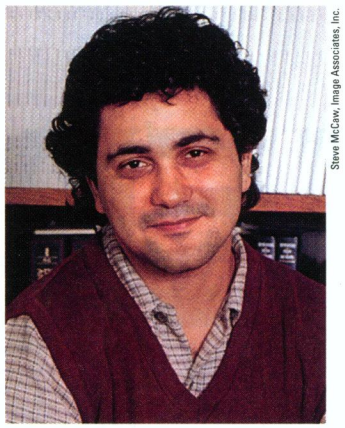
Greg Blumenthal

Design Issues

Issues surrounding how to set up experiments and which experiments to perform play a fundamental role in advances of both existing and new approaches. CoBRA researchers believe that an experiment's design must meet two criteria. First, it must be scientifically clean, meaning it must produce a clear answer to a specific question. Second, Portier says, "If there is a positive finding from a study, a regulatory agency should be able to use that information in the assessment of human risks from human exposures and talk about whether the chemical is going to be an important problem in the environment. It's clear that we want our mechanistic data to be of utility to [such agencies]."

At the NIEHS, any researcher working with a chemical that has been nominated to the NTP for testing who wants help with design issues can turn to the Toxicokinetics Group within CoBRA. The group routinely meets with 15–20 NIEHS scientists who form the Toxicokinetics Faculty holds monthly meetings to go over experimental protocols, with emphasis on toxicokinetics—the quantitative description of the absorption, distribution, metabolism, and elimination of toxic chemicals.



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Hisham El-Masri

The Toxicokinetics Group investigates two categories of chemicals: chemicals that were nominated to the NTP before the faculty's existence, and newly nominated ones. For prefaculty chemicals that are nearly ready for peer review of the NTP's technical reports on them, toxicokinetics can be used to help explain the sex and species differences in effects caused by a chemical. Greg Blumenthal, a CoBRA trainee and executive secretary of the faculty, says, "On the chemicals in the earlier stages, toxicokinetic modeling is very valuable as a tool in helping design the toxicology, helping to set it up correctly. The toxicology studies . . . are big, ungainly things that you don't want to go through twice. Toxicokinetic modeling is relatively quick and cheap, and it gives a fairly decent amount of information in helping to put the toxicology study together correctly."

Ten years ago, the NTP concentrated on toxicity studies such as cancer bioassays and immunotoxic effects. In other words, the NTP examined *what* a chemical did, but not *how* it did it. In the last five years, the NTP has started looking for the mechanisms behind a chemical's effects, which relies precisely on the strength of toxicokinetics data and modeling.

Future Goals

According to Portier, risk-assessment managers need better information because "95% of risk assessment is done on the back of an envelope—someone has very limited information, has to make a decision today, and uses the best judgment from the available information." In the future, Portier thinks that CoBRA could provide a risk-assessment manager with the best technical guidance and easily accessible analytical tools to make a very quick decision on a compound's risk.

Nevertheless, so many potentially dangerous chemicals exist that they cannot all be tested in any reasonable period of time. The U.S. Toxic Substances Control Act includes nearly 70,000 entries, but the NTP can test only about 40 chemicals a year. So it would take more than 1,700 years to test them all and the list grows by about 2,000 chemicals each year. Fortunately, knowing the potential risk of one chemical helps scientists predict the risk of others. Says Portier, "Certain compounds have patterns of toxicity response that are similar. The ideal would be to start isolating these patterns to aid in making decisions."

Mike May